Reconsideration of the rejections is respectfully requested. By the present amendment, claims 22-44, 51, 52, 56 and 58 are amended, new claims 60-64 are presented, and claims 26-27, 29-31, 33-35, 37-39, 41, 42 and 43 are cancelled. Thus, claims 22-25, 30, 32, 36, 40 and 44-64 are under examination.

Prior to the amendment, fees for a total of 54 claims including 5 independent claims and one or more multiple dependent claims had been paid for. By the present amendment there are a total of 41 claims including 6 independent claims and at least one multiple dependent claim. Therefore, no claim fees are believed to be due. However, should the Office determine that any additional fees are required for consideration of this paper, the Office is authorized to charge Deposit Account No. 04-0480.

Various claims have been amended to more clearly define the invention. Support for the amendments is either apparent, or is as described in the text below. Support for the recital of sequence relatedness in various claims can be found, for example, at page 14, lines 1-9. The "substitution, deletion or insertion" language finds support, for example, at page 13, lines 4-9 and page 14, lines 21-25. The relatedness language in the claims disallows any change which could be interpreteted to create a change at corresponding positions of more than 20%, as recited on page 14, line 4 of the specification. The "less than 25 amino acids" recitation finds support at page 9, lines 22-26. The "conjugate" language finds support, for example, at page 10, lines 16-18. It is respectfully submitted that the amendments add no new matter.

Drawings

The objections to the drawings will be addressed upon the issuance of a Notice of Allowance.

Claim Rejections - 35 U.S.C. §112, First Paragraph

Claims 22-57 stood rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an enabling disclosure. As discussed below, Applicants respectfully traverse the rejection.

In support of this rejection, the Office Action sets forth a number of arguments in pages 2-7. For instance, the Office Action asserts that the disclosure does not support the breadth of the claimed invention as follows:

> (1) The disclosure fails to provide sufficient guidance or direction pertaining to acceptable amino acid replacements, additions, or deletions the CTL epitope

that will retain the MHC-restricted CTL response. The prior and present art teach that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule (Smith et al., 1997; Bertoletti et al., 1994; Johnson et al., 1992; Couillin et al., 1995; and, Hahn et al., 1992). Additionally, applicants themselves state (refer to page 5 of the disclosure) that "At the present time, it is difficult to predict from the sequence of an antigenic protein how the protein will be processed and which peptide portions will bind HLA class I molecules and be presented to CTL's. Binding motifs have been predicted for some HLA class I molecules based on sequence analysis of peptides eluted from these molecules . . . However, not all peptides that match the motif will be recognized as CTL-recognizable epitopes. Moreover, even of the peptides that are processed and bind to HLA class I molecules, identifying which ones will contain CTL-recognizable epitopes is not yet predictable." Without any prior instruction, which amino acid substitutions could one practicing the invention introduce directly into the CTL epitope and still retain an MHC Class I-restricted CTL response?

(2) The disclosure fails to provide sufficient guidance or direction concerning the affects of amino acid substitutions, additions, or deletions on sequences flanking the disclosed CTL epitopes. The prior art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation (Del Val et al., 1991; Hahn et al., 1992; and, Eisenlohr et al., 1992). As described in the preceding paragraph, it is difficult to predict what amino acid sequences are required for proper peptide processing by the host and how they influence CTL recognition and lysis. Eisenlohr et al. (1992) reported that CTL epitopic flanking amino acid residues were critical for the efficient processing and presentation of antigen to CTL. Flanking sequences were capable of either enhancing or abrogating peptide processing and recognition. Hahn et al. (1992) disclosed that a single amino acid substitution immediately flanking the recognized CTL epitope significantly curtailed CTL-mediated cell lysis. Additional CTL studies performed by Del Val et al. (1991) documented that "residues that directly flank the antigenic sequence in a protein critically influence the amount of naturally processed and presented antigenic peptide." Moreover, the art also teaches that mutations in CTL epitopes adversely affect extracellular antigen processing by altering the trimming of flanking residues in longer sequences and influencing the susceptibility of optimal epitopes to proteolytic degradation (Smith et al., 1997; Del Val et al., 1991; Eisenlohr et al., 1992). In the absence of further guidance how would one practicing the invention reasonably predict which amino acid substitutions, additions, and/or deletions, will result in retention of the desired immunologic properties of any given peptide?

The answer to this criticism is that Applicants have identified the core structure of the molecules of interest and recited in their claims that a modest amount of substitution, deletion or insertion is allowable in this core structure. These core structures were uncovered from a far larger pool of candidate core structures, the bulk of which proved less effective. This was the challenge mentioned in the above-quoted text taken from the specification. However, this aspect of the challenge has been met by the teachings in the specification, which teachings yield the core structures. The effect of any substitution, deletion or insertion in the core structures can be

determined by ordinary, not undue, experimentation, as illustrated by the discussion of how to find other active peptides from the core structures (found on pages 11-17) and supported by the methodology taught in Examples 1-6.

As to the identified core structures, the specification is replete with guidance on conservative strategies for making substitutions. See, for example, page 12, line 33 through page 15, line 36. Moreover, Applicants respectfully submit that the amount of substitution, deletion or insertion permissible is modest so that, given the tools available to the molecular biologist at the time of filing, experimenting with these variations and using the tools taught in the specification to confirm activity does not present a need for undue experimentation.

Applicants further respectfully submit that the lessons of the above-cited literature do not imply that undue experimentation is required to practice the invention within its claimed scope. Eisenlohr does teach that flanking sequence can be important. But the standard for enablement is whether the invention can be practiced without undue experimentation, and substantial experimentation can be acceptable if it is routine in the relevant art. Hahn notes that "[m]ost alterations in residues flanking the endogenously expressed epitope do not appreciable affect the generation and recognition of the site [i.e., epitope]." Thus, the Office Action focuses on lessons in Hahn that present exceptions to the general rule taught in Hahn. Applicants respectfully submit that even if some sites are highly restrictive in the amount of substitution, deletion or insertion allowed, the invention can nonetheless be practice without *undue* experimentation. *See, e.g., In re Wands*, 858 F.2d 731, 749 (Fed. Cir. 1988), where the Federal Circuit, discussing the analogous art searching for monoclonal antibody producing hybridomas, noted that the failures encountered in such searches do not indicate undue experimentation. Del Val teaches one insertion site in a construct for making fusion proteins reduced the activity of a 9-mer *but not the activity of a corresponding 18-mer having native flanking sequence.* Del Val also provides guidance to the effect that alanine residues at the immediate flanks can ameliorate presentation difficulties such as are found, in one context, for the 9-mer. Thus, Del Val in fact provides guidance for useful avenues to practice the invention to its claimed scope.

The Office Action has further assertions about the specification's alleged failures to teach how make the invention. To one such assertion, Applicants respond that the applicable legal standard does not require that the disclosure teach all substitutions, deletions or insertions that can be expected to function, since the legal standard very expressly allows for reasonable experimentation. Not reciting every operable species of the invention does not offend Section

112 either, even in an unpredictable art. M.P.E.P. § 2164.03. Nor is there a requirement that all possible polypeptides be screened. The fact that practitioners of the relevant art, which includes drug discovery, are prepared to screen negative species of polypeptides in order to find one that has the desired CTL-activating characteristics further supports enablement of required, even extensive, experimentation. The literature of record is replete with evidence of such willingness, as is indicated for example by the substantial amount of mapping conducted by Reece et al., *J. Immunol.* 151:6175-6184, 1993. Time and difficulty of experiments are not determinative if they are merely routine. M.P.E.P. § 2164.06. Whether a person screening for further embodiments of the present invention would continue until all possible embodiments were found should have no bearing on the question of enablement here because it would be "unlikely that undue experimentation would be defined in terms of the number of [possible polypeptides] that were never screened." *Wands*, at 858 F.2d at 740.

Applicants have recited operative embodiments of the claimed invention and the skilled artisan in the art has available clear teachings as to the criteria for alternative embodiments and has clear teachings on methods by which to screen such alternative embodiments. Thus, only routine experimentation is required to practice this invention. Accordingly, in view of the teachings provided in the specification, and the fact that modification of a known peptide is routine, Applicants respectfully submit that the subject matter of the claims is fully enabled by the specification and the enablement rejection must be withdrawn

To the assertion that Applicants have only identified motifs, Applicants submit that they have identified from many choices having a MHC class I motif a very limited set of peptides that do bind class I molecules, and that they have focused their claims around these concrete findings. Moreover, Applicants respectfully submit there is no reasonable basis for the suggestion that the above-quoted text from the specification implies that the skilled artisan cannot reasonably make the determination that certain peptides bind MHC class I molecules; the specification teaches how make this determination.

Next, the Office Action asserts that the specification fails to teach examining immunogenicity. The specification, however, teaches testing for cytotoxicity. See pages 50-56 of the specification. The Table on page 55 confirms that a broad assortment of the claimed peptides are cytotoxic.

Finally, this section of the Office Action presents an attack on the clinical efficacy of the claimed formulations. This discussion brings into play the now well-developed limitations on the Patent Office's role in considering utility issues. Under the utility guidelines of MPEP 2107,

Applicants are due a presumption of their asserted utility. "If the asserted utility is credible (i.e., believable based on the record or nature of the invention), a rejection based on 'lack of utility' is not appropriate." MPEP 2107.01(c)(i). Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use satisfies the utility requirement. MPEP 2107(c). Applicants illustrated peptides clearly have pharmacological activity, as indicated by Applicants' exemplification of CTL responses.

Accordingly, given the explicit teachings in the specification and the state-of-the-art, Applicants respectfully submit that one of ordinary skill can practice the invention to its claimed scope without undue experimentation.

Claims 58 and 59 stood rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an enabling disclosure. These claims relate to a pharmaceutical composition having a peptide that induces an hepatitis C virus (HCV)-specific response in cytotoxic T lymphocytes. Applicants respectfully traverse the rejection. This rejection is addressed by the above discussion on utility. Further, Applicants respectfully protest this assertion of a rejection for want of utility which is framed without regard to the utility guidelines. The Office expended considerable effort, memorialized in these guidelines, to differentiate the utility requirement from the regulatory requirements of the Food and Drug Administration. Applicants respectfully submit that the claimed invention meets the requirements of the utility guidelines. Applicants respectfully point out that the utility requirement is met with evidence of pharmacological activity, such that Applicants are not called upon to show a vigorous HCV-specific CTL response. If Applicants seek to market a composition of claim 58 or 59, the Food and Drug Administration will address the question of whether such a composition is effective enough in eradicating virus, or otherwise providing a clinical benefit.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claims 22-59 are rejected under 35 U.S.C. §112, second paragraph, for failing to distinctly claim the subject matter of the claimed invention. In particular, the Office Action asserts that the recitation of "about 20%" and the reference to differences in sequence in various claims is vague and indefinite. In light of certain clarifying amendments to the pertinent claims, Applicants respectfully submit that these rejections should no longer apply.
Accordingly, Applicants respectfully submit that the rejections under 35 U.S.C. §112, second paragraph, should be withdrawn.

Double Patenting - 35 U.S.C. §101

Claims 27, 29, 31, 33, 35, 37, 39, 41 and 43 stood rejected under the statutory type double patenting, otherwise termed same invention type double patenting. In light of the cancellation of these claims, Applicants respectfully submit that this rejection should not apply to the claims as presented herein. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. §101 should be withdrawn.

Double Patenting - Non-statutory

Claims 22-26, 28, 30, 32, 34, 36, 38, 40, 42, and 44-59 stood rejected under the obviousness-type double patenting as being unpatentable over claims 1 and 11-33 of U.S. Patent No. 5,709,995. A terminal disclaimer as to those claims at issue will be filed at the time of the issuance of a Notice of Allowance. Accordingly, Applicants respectfully submit that the obviousness-type double patenting rejection should be withdrawn.

Conclusion

In view of these amendments and remarks, Applicants respectfully submit that the application is in condition for allowance. Accordingly, reconsideration and allowance are respectfully solicited.

Respectfully submitted,

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